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(71) Applicants *(for all designated States except US)*: **SHANGHAI INSTITUTE OF MATERIA MEDICA, CHINESE ACADEMY OF SCIENCES** [CN/CN]; Zu chong-zhi Road 555, Zhangjiang Hi-Tech Park, Pudong, Shanghai, People's Republic of China (CN). **LES LABORATOIRES SERVIER** [FR/FR]; 12, Place de la Défense, F-92415 Courbevoie Cédex (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **QIN, Guo-Wei** [CN/CN]; Room 907, No. 1, Lane 69, Tian-Yue-Quiao Road, 200030 Shanghai, People's Republic of China (CN). **TANG, Xi-Can** [CN/CN]; Room 609, No.800, Cao-Xi-Bei Road, 200030 Shanghai, People's Republic of China (CN). **WANG, Rui** [CN/CN]; Room 501, N°1, Lane 1717, Xi-Zang-Nan Road, 200030 Shanghai, People's Republic of China (CN). **ZHOU, Tian-Xi** [CN/CN]; Room 1208, N°2, Lane 69, Tian-Yue-Qiao Road, 200030 Shanghai, People's Republic of China (CN). **LESTAGE, Pierre** [FR/FR]; 9 Allée de la Grande Terre, F-78170 La Celle Saint Cloud (FR). **CAIGNARD, Daniel-Henri** [FR/FR]; 22, avenue de la République, F-78203 Le Pecq (FR). **RENARD, Pierre** [FR/FR]; 3, avenue du Parc, F-78150 Le Chesnay (FR).

(74) Common Representative: **LES LABORATOIRES SERVIER**; 12, Place de la Défense, F-92415 Courbevoie Cédex (FR).

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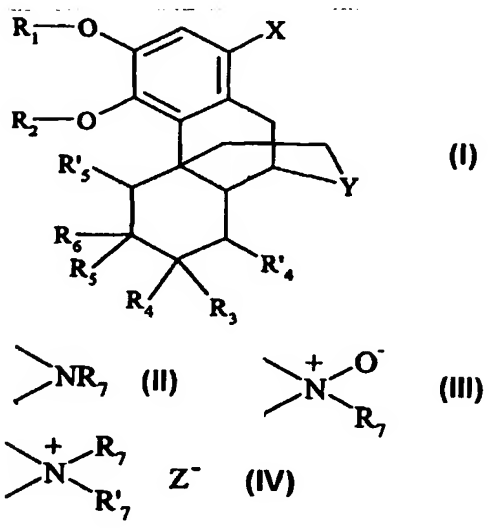
(54) Title: SINOMENINE AND SINOMENINE COMPOUNDS, SYNTHESIS AND USE



(I)

(II)

(III)

(IV)

(57) Abstract: The invention relates to sinomenine and compounds thereof and also to compounds of formula (I), wherein R_1 represents an alkyl group; R_2 represents a hydrogen atom or an alkylcarbonyl group, an haloalkylcarbonyl group or an arylcarbonyl; Y represents a group (II), (III) or (IV); R_3 ,R_4, R'_4, R_5, R'_5 and R_6 are as defined in the description; and X represents a halogen atom. Medicaments.

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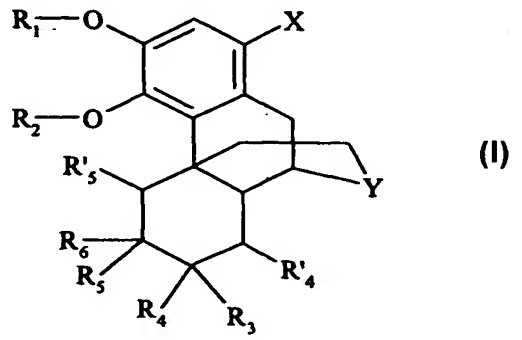
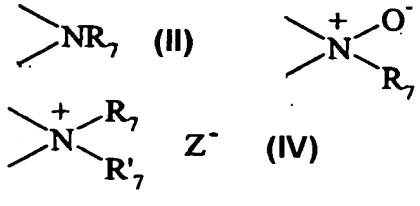


(I)



(II) (III)

(IV)

(57) Abstract: The invention relates to sinomenine and compounds thereof and also to compounds of formula (I), wherein R_1 represents an alkyl group; R_2 represents a hydrogen atom or an alkylcarbonyl group, an haloalkylcarbonyl group or an arylcarbonyl; Y represents a group (II), (III) or (IV); R_3 ,R_4, R'_4, R_5, R'_5 and R_6 are as defined in the description; and X represents a halogen atom. Medicaments.

WO 2004/048340 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

SINOMENINE AND SINOMENINE COMPOUNDS, SYNTHESIS AND USE

Sinomenum acutum is a plant taking the form of a ligneous liana, which is widespread in the centre, South-East and South-West of China and is included in the Chinese Pharmacopoeia (Pharmacopoeia Committee of People's Republic of China, 2000). It contains a large number of alkaloids of various chemical structures, such as sinomenine, sinoacutine, ethylsinomenine, disinomenine, tetrahydroepiberberine, tuduranine and magnoflorine (Huang Tai-Kang, « *Handbook of the Composition and Pharmacology of Common Chinese Drugs* », Chinese Medical Science and Technology Publisher, 1994, Beijing, 1156-1160).

Sinomenine, a morphine-like alkaloid and a major constituent of the plant, has been much studied; in particular, it has been possible to demonstrate anti-inflammatory, immunosuppressive, anti-arrhythmic and analgesic properties (Qiang Liu *et al.*, Chinese Traditional and Herbal Drugs, 1997, 28(4), 247).

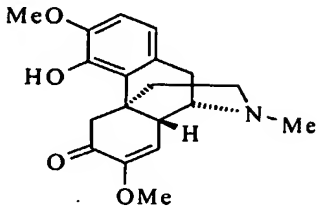
We have now discovered that sinomenine has mnemocognition-facilitating properties in animal experimental models.

Ageing of the population due to increased life expectancy has brought with it a major increase in cognitive disorders associated with normal cerebral ageing or pathological cerebral ageing occurring in the course of neurodegenerative diseases such as, for example, Alzheimer's disease.

The majority of substances used today in treating cognitive disorders associated with ageing act by facilitating the central cholinergic systems – either directly, as in the case of acetylcholinesterase inhibitors (tacrine, donepezil) and cholinergic agonists (nefiracetam), or indirectly, as in the case of nootropic agents (piracetam, pramiracetam) and cerebral vasodilators (vinpocetine).

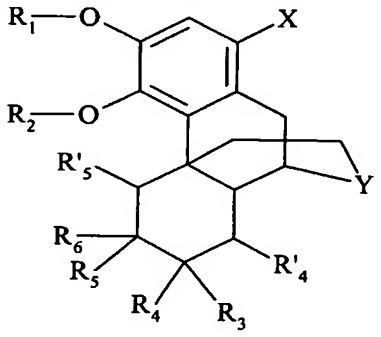
It has been therefore been especially valuable to synthesise new compounds that are capable of opposing the cognitive disorders associated with ageing and/or of improving cognitive processes.

The present invention relates, on the one hand, to the use of sinomenine :



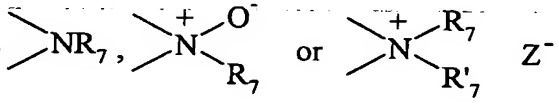
and/or sinomenine compounds in mnemocognitive disorders and, on the other hand, to the synthesis of new compounds having especially valuable pharmacological properties in the same area.

The present invention relates more specifically to compounds of formula (I) :



(I),

wherein

- R_1 represents an alkyl group,
- R_2 represents a hydrogen atom or an alkylcarbonyl group, an haloalkylcarbonyl group or an arylcarbonyl group,
- Y represents a group 

  wherein R_7 and R'_7, identical or differents, each represent an alkyl group, and Z^- represents a halogen anion,
- R_3 represents a hydroxy or alkoxy group,
- R_4 and R'_4 each represent a hydrogen atom or together form an additional bond, or R_3 and R_4 together form an oxo or =N-OR_8 group (wherein R_8 represents a hydrogen atom or an alkyl group),

- R_6 represents a hydroxy, alkylcarbonyloxy (wherein the alkyl moiety can be substituted by a hydroxy, alkoxy, carboxy or alkyloxycarbonyl group) or alkoxy group,
- R_5 and R'_5 each represent a hydrogen atom or together form an additional bond, or R_5 and R_6 together form an oxo, =N-OR_9 or =N-$NR_{10}R_{11}$ group (wherein R_9, R_{10}, and R_{11}, which may be the same or different, each represent a hydrogen atom or an alkyl group),
- and X represents a halogen atom,

with the proviso that the compound of formula (I) cannot represent 1-bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one,

it being understood that

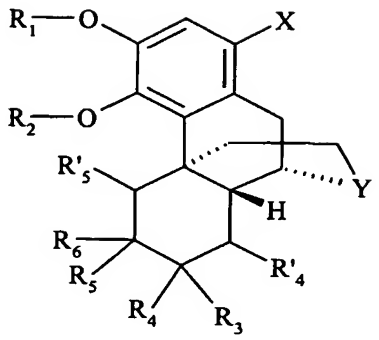
- "alkyl" means an alkyl group containing 1 to 6 carbon atoms which may be linear or branched,
- "alkoxy" means an alkyloxy group containing 1 to 6 carbon atoms which may be linear or branched,

to their enantiomers and diastereoisomers, and to addition salts thereof with a pharmaceutically acceptable acid or base.

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, methanesulphonic acid, camphoric acid, oxalic acid etc..

Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine etc..

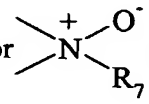
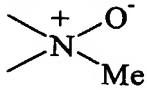
The preferred configuration of compounds of formula (I) according to the invention is that shown in formula (I'):



(I')

The preferred group R_1 is the methyl group.

Advantageously, R_2 represents a hydrogen atom or a group EtCO and more preferably a hydrogen atom.

Y represents, preferably, a group NR_7 or  and, more especially, a group N-Me or  .

X represents, very preferably, a chlorine or bromine atom.

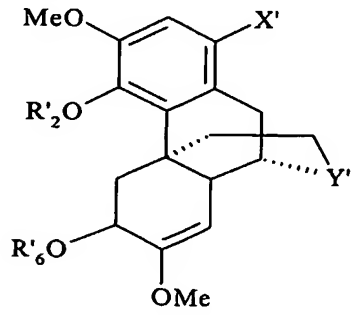
Advantageously, the invention relates to compounds of formula (I) wherein R_3 represents an alkoxy group and R_4 and R'_4 together form an additional bond.

The preferred meaning of R_5 is a hydrogen atom.

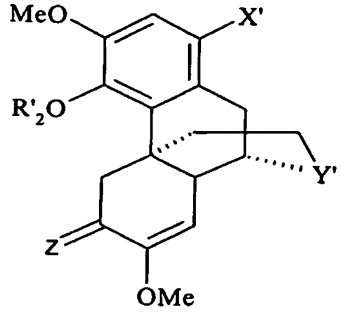
R_6 represents advantageously an OH, ethoxy or alkylcarbonyloxy group and, more especially, ethylcarbonyloxy.

Another interesting aspect of the invention is compounds of formula (I) for which R_5 and R_6 form together an oxo group or an $=N-OH$ group.

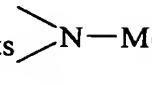
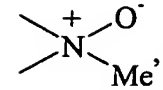
Very preferably, the invention relates to compounds of formula (I") and (I'") :



(I") and



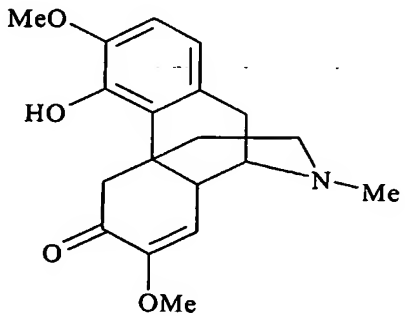
(I'")

wherein Y' represents  or  , R'_2 and R'_6, which may be the same or different, represent a hydrogen atom or an alkylcarbonyl group, X' represents a chlorine or bromine atom and Z represents $=O$ or $=N-OH$.

Even more preferably, the invention relates to compounds of formula (I) that are (9α,13α)-1-chloro-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol, (9α,13α)-1-chloro-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate, (9α,13α)-1-bromo-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol, (9α,13α)-1-bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime, (9α,13α)-1-bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide, (9α,13α)-1-chloro-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide.

The enantiomers and diastereoisomers and addition salts with a pharmaceutically acceptable acid or base of the preferred compounds of the invention form an integral part of the invention.

The invention relates also to a process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting material the compound of formula (II) :



(II),

obtained by extraction starting from the stem of *Sinomenum acutum* according to Figure 1 below :

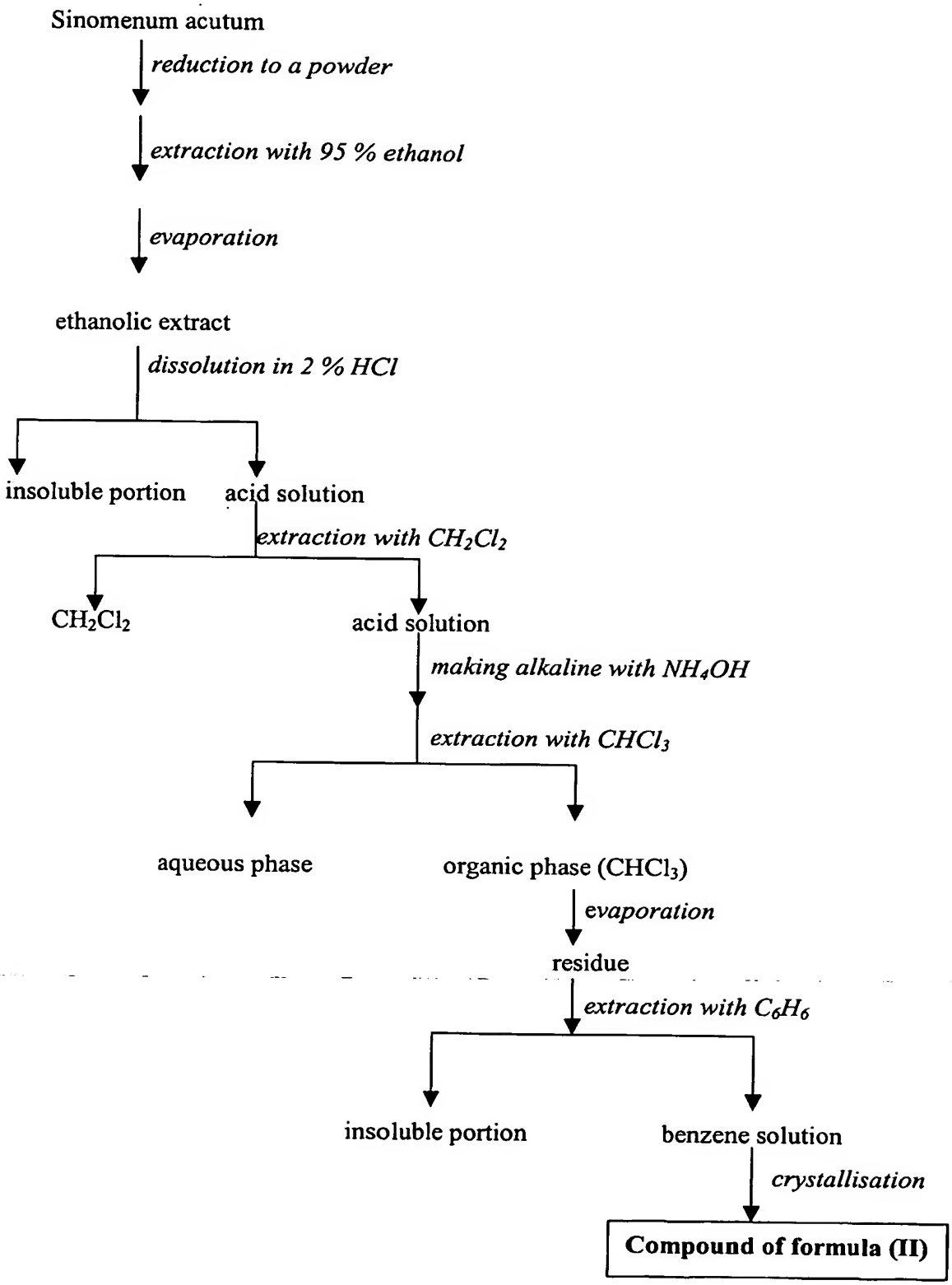
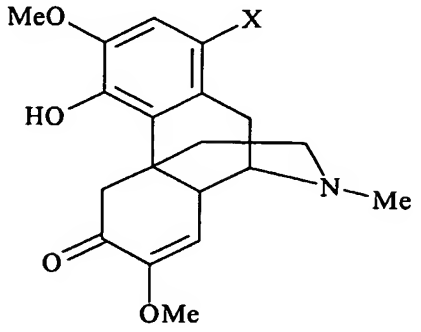


Figure 1 *: Extraction of the compound of formula (II)*

which is subjected to the action of a halogenating agent such as SO_2Cl_2 or Br_2 to obtain the compound of formula (I/a), a particular case of the compounds of formula (I):



(I/a),

wherein X is as defined for formula (I), which compound of formula (I/a) is subjected to conventional chemical reactions to obtain the totality of the compounds of formula (I), which may be purified according to a conventional separation technique, are converted, if desired, into their addition salts with a pharmaceutically acceptable acid or base and are separated, where appropriate, into their isomers according to a conventional separation technique.

Besides the fact that the compounds of the present invention are new, they possess properties of facilitating cognitive processes, making them of use in the treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

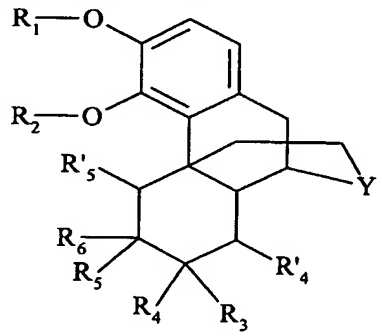
The invention relates also to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I) together with one or more appropriate, inert, non-toxic excipients.

The Applicant has moreover discovered that sinomenine and/or sinomenine compounds have mnemocognition-facilitating properties.

The invention accordingly relates also to the use of sinomenine and/or sinomenine compounds in obtaining pharmaceutical compositions for use in the treatment of cognitive

deficiencies associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

More especially, the invention relates to the use, in obtaining pharmaceutical compositions for use in the treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases, of sinomenine and/or sinomenine compounds such as, for example, the compounds of formula (Ia) :



(Ia),

wherein R_1, R_2, R_3, R_4, R'_4, R_5, R'_5, R_6 and Y are as defined for formula (I), and, more especially, of (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one hydrazone; (7α,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; (7β,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; (9α,13α)-3,7-dimethoxy-17-methyl-6-oxo-7,8-didehydromorphinan-4-yl propionate; (9α,13α)-3,4,7-trimethoxy-17-methyl-7,8-didehydromorphinan-6-one; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime; (9α,13α)-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide; (9α,13α)-6-amino-3,7-dimethoxy-17-methylmorphinan-4-ol; 4-{[(9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl]-oxy}-4-oxobutanoic acid; (9α,13α)-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate; (9α,13α)-17-benzyl-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-17-ium-6-one bromide; (9α,13α)-17-ethyl-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-17-ium-4,6-diol bromide; (9α,13α)-17-ethyl-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-17-ium-6-one bromide; (9α,13α)-4-(benzoyloxy)-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl benzoate; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl

benzoate; (9α,13α)-6-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4-yl benzoate.

An advantageous aspect of the invention relates to the use of sinomenine in obtaining pharmaceutical compositions for use in the treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases.

Another especially interesting aspect of the invention relates to the use, in obtaining pharmaceutical compositions for use in the treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases, of compounds of formula (Ia) and, more especially, of (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one hydrazone; of (7α,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; of (7β,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; of (9α,13α)-3,7-dimethoxy-17-methyl-6-oxo-7,8-didehydromorphinan-4-yl propionate; of (9α,13α)-3,4,7-trimethoxy-17-methyl-7,8-didehydromorphinan-6-one; of (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime; of (9α,13α)-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol; of (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide; of (9α,13α)-6-amino-3,7-dimethoxy-17-methylmorphinan-4-ol; of 4-{[(9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl]oxy}-4-oxobutanoic acid; of (9α,13α)-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate; of (9α,13α)-17-benzyl-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-17-ium-6-one bromide; of (9α,13α)-17-ethyl-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-17-ium-4,6-diol bromide; of (9α,13α)-17-ethyl-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-17-ium-6-one bromide; of (9α,13α)-4-(benzoyloxy)-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl benzoate; of (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl benzoate; of (9α,13α)-6-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4-yl benzoate.

The invention relates also to pharmaceutical compositions comprising sinomenine or a compound thereof, in combination with one or more pharmaceutically acceptable

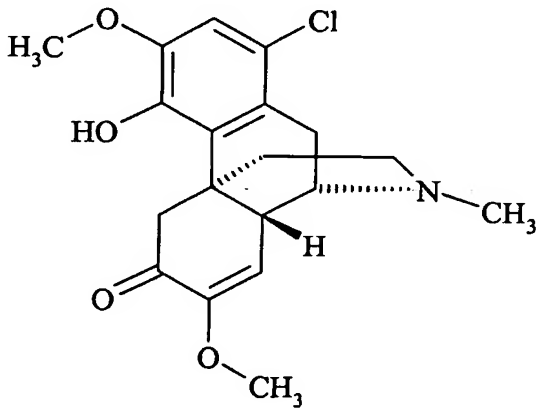
excipients, for use in the treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions etc..

The useful dosage can be varied according to the nature and severity of the disorder, the administration route and also the age and weight of the patient. The dosage varies from 0.01 mg to 1 g per day in one or more administrations.

The following Examples illustrate the invention but do not limit it in any way.

EXAMPLE 1 : (9α,13α)-1-Chloro-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one



To a solution of 100 mg of the compound of formula (II) in 5 ml of $CHCl_3$ there are added 3 drops of SO_2Cl_2. The reaction mixture is stirred at ambient temperature for 4 hours and the pH is adjusted to 7-8 with $NaHCO_3$ solution; extraction with $CHCl_3$ is then carried out. The organic phase is evaporated under reduced pressure and the residue obtained is

chromatographed on silica gel using an eluant $CHCl_3$-MeOH (9 : 1) to yield the title compound in the form of a yellowish solid.

Melting point : 126-128°C.

EXAMPLE 2 : (9α,13α)-1-Chloro-3,7-dimethoxy-17-methyl-6-oxo-7,8-didehydro-morphinan-4-yl propionate

To a solution of 500 mg of the compound obtained in Example 1 and 100 mg of DMAP in 15 ml of pyridine there are slowly added 2 ml of propionic anhydride, and the reaction mixture is stirred at ambient temperature for 3 hours. The reaction mixture is then evaporated and the residue obtained is dissolved in a small volume of water. The solution obtained is adjusted to pH = 8-9 with $NaHCO_3$ solution and is then extracted with $CHCl_3$. The organic phase is washed 3 times with water, dried over sodium sulphate and evaporated. The residue obtained is chromatographed on silica gel using an eluant $CHCl_3$-MeOH (20 : 1) to yield the title compound in the form of a colourless oil.

EXAMPLE 3 : (6β,7β,9α,13α)-1-Chloro-3,7-dimethoxy-17-methylmorphinan-4,6-diol

A mixture of 720 mg of compound of Example 1 and 100 mg of PtO_2 in 50 ml of absolute ethanol is stirred at room temperature under H_2 atmosphere for 12 hours. The PtO_2 is removed by filtration and the ethanol is evaporated in vacuum to give a syrupy residue. This residue is washed with hot absolute ethanol (10 ml) to give a powdery solid which is collected by filtration and crystallized in $CHCl_3/C_2H_5OH$ to give the title compound in the form of white crystals.

Melting point : 210-212°C.

EXAMPLE 4 : (9α,13α)-1-Chloro-3,7-dimethoxy-17-methyl-7,8-didehydro-morphinan-4,6-diol

To a solution of 500 mg of the compound obtained in Example 1 in 15 ml of methanol there are added 500 mg of $NaBH_4$, and the reaction mixture is stirred for 1.5 hours. The

methanol is then evaporated off and the residue obtained is extracted with $CHCl_3$. The organic phase is dried over Na_2SO_4 and evaporated under reduced pressure. The title compound is obtained in the form of white crystals, by recrystallisation from Et_2O.
Melting point : 118-120°C.

EXAMPLE 5 : (9α,13α)-1-Chloro-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate

The title compound is obtained using the procedure described for Example 2, starting from the compound obtained in Example 4.
Oil.

EXAMPLE 6 : (6β,7β,9α,13α)-1-Chloro-3,7-dimethoxy-17-methyl-4-(propionyloxy)-morphinan-6-yl propionate

The title compound is obtained using the procedure described for Example 2, starting from the compound obtained in Example 3.
Oil.

EXAMPLE 7 : (9α,13α)-1-Chloro-3,4,7-triméthoxy-17-methyl-7,8-didehydro-morphinan-6-one

A solution of 400 mg of the compound of Example 1 in 10 ml of methanol is treated with an excess of a freshly made preparation of diazomethane in ether, and the reaction mixture is stirred at ambient temperature for 12 hours. The excess of diazomethane is then broken down using glacial acetic acid, and the solvents are evaporated off under reduced pressure. The residue obtained is adjusted to pH = 8-9 using saturated $NaHCO_3$ solution and is then extracted with $CHCl_3$. The organic phase is dried over Na_2SO_4 and evaporated *in vacuo*, and the residue obtained is chromatographed on silica gel (eluant $CHCl_3$-MeOH) to yield the title product in the form of an oil.

EXAMPLE 8 : (9α,13α)-1-Chloro-3,4,7-trimethoxy-17-méthyl-7,8-didehydro-morphinan-6-ol

The title compound is obtained using the procedure described for Example 4, starting from the compound obtained in Example 7.

Colourless crystals.

Melting point : 163-165°C.

EXAMPLE 9 : (9α,13α)-1-Chloro-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime

To a solution of 360 mg of the compound obtained in Example 1 in ethanol there are added 200 mg of NH_2OH . HCl and 300 mg of sodium acetate. The reaction mixture is stirred for 4 hours; it is then filtered and evaporated under reduced pressure. The residue obtained is made alkaline using $NaHCO_3$ solution and extracted with $CHCl_3$. The organic phase is dried over Na_2SO_4 and then evaporated under reduced pressure, and the title compound is obtained in the form of needles, by recrystallisation from EtOH.

Melting point : 167-169°C.

EXAMPLE 10 : (9α,13α)-1-Chloro-6-ethoxy-4-hydroxy-3-methoxy-17-methyl-5,6-didehydromorphinan-7-one

To a solution of 1.3 g of the compound obtained in Example 1 in 100 ml of $CHCl_3$ and 10 ml of absolute alcohol there is added SO_2Cl_2 at 10°C, and the reaction mixture is stirred for 8 hours. The solvent is then evaporated off under reduced pressure, and the residue is neutralised using $NaHCO_3$ and then extracted with $CHCl_3$. The organic phase is dried over Na_2SO_4 and evaporated under reduced pressure, and the title compound is obtained in the form of yellowish crystals, by recrystallisation from CH_3CN.

Melting point : 190-192°C.

EXAMPLE 11 : (9α,13α)-1-Chloro-4-hydroxy-3,7-dimethoxy-17-méthyl-7,8-didehydromorphinan-6-one hydrazone

A solution of 600 mg of the compound obtained in Example 1 in 10 ml of 85 % hydrazine is stirred at 90°C for 8 hours. After cooling, the reaction mixture is filtered and the solid obtained is washed with water and recrystallised from EtOH to yield the title compound in the form of yellowish crystals.

Melting point : 235-237°C.

EXAMPLE 12 : (9α,13α)-1-Bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one

A solution of 6.6 g of the compound obtained in Example 1 in 150 ml of $CHCl_3$ is cooled to 0°C, and bromine dried over concentrated sulphuric acid is added dropwise, with stirring, whilst maintaining the reaction mixture at 5°C. The reaction is continued for a few minutes and then neutralisation is carried out using $NaHCO_3$. The organic phase is separated off, dried over Na_2SO_4 and evaporated under reduced pressure, and the residue obtained is recrystallised from EtOH to yield the title compound in the form of brown crystals.

Melting point : 163-165°C.

EXAMPLE 13 : (9α,13α)-1-Bromo-3,7-dimethoxy-17-methyl-7,8-didehydro-morphinan-4,6-diol

The title compound is obtained using the procedure described for Example 4, starting from the compound obtained in Example 12 and replacing $NaBH_4$ by KBH_4.

Solid.

Melting point : 144-146°C.

EXAMPLE 14 : (9α,13α)-1-Bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one hydrazone

The title compound is obtained using the procedure described for Example 11, starting from the compound obtained in Example 12.

Solid.

Melting point : 208-210°C.

EXAMPLE 15 : (9α,13α)-1-Bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime

The title compound is obtained using the procedure described for Example 9, starting from the compound obtained in Example 12.

Solid.

Melting point : 180-182°C.

EXAMPLE 16 : (9α,13α)-1-Bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide

A mixture of compound of Example 12 (820 mg) in H_2O_2 (10 ml) is stirred at room temperature for 24 hours and then extracted with $CHCl_3$ three times (30 ml X 3). The combined extracts are dried overnight with anhydrous Na_2SO_4 and the solvent is removed by evaporation to give a residue to which are added 30 ml of cold water. The powdery solid is collected by filtration, washed with cold water until the water being colorless, and crystallized in ethanol to give the title compound as a solid.

Melting point : 170-172°C.

EXAMPLE 17 : (9α,13α)-1-Chloro-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide

A mixture of compound of Example 1 (720 mg) in H_2O_2 (10 ml) is stirred at room temperature for 24 hours and then extracted three times (25 ml X 3). The combined

extracts are dried over anhydrous Na_2SO_4 and the solvent is removed by evaporation. 30 ml of cold water are added to the residue obtained and the resulting powdery white solid is collected by filtration and crystallized in ethanol to give the title compound as a solid.
Melting point : 170-172°C.

EXAMPLE 18 : (9α,13α)-1-Bromo-3,7-dimethoxy-17-methylmorphinan-4,6-diol

The title compound is obtained using the procedure described for Example 3, starting from the compound obtained in Example 12.
Melting point : 160-162°C.

EXAMPLE 19 : (9α,13α)-1-Chloro-6-ethoxy-3-methoxy-17-methyl-5,6-didehydro-morphinan-4,7-diol

The title compound is obtained using the procedure described for Example 4, starting from the compound obtained in Example 10 and replacing $NaBH_4$ by KBH_4.
Solid.
Melting point : 168-170°C.

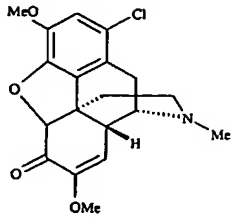
EXAMPLE 20 : (9α,13α)-1-Chloro-6-ethoxy-4-hydroxy-3-methoxy-17-methyl-5,6-didehydromorphinan-7-one oxime

The title compound is obtained using the procedure described for Example 9, starting from the compound obtained in Example 10.
Solid.
Melting point : 216-218°C.

EXAMPLE 21 : (9α,13α)-17-Benzyl-1-bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-17-ium-6-one bromide

The title compound is obtained from compound of example 12 subjected to the action of benzylbromide.

Melting point : 190-192°C.

EXAMPLE 22 : 

The title compound is obtained after treatment of compound of Example 1 in basic medium.

Melting point : 204-206°C.

EXAMPLE 23 : (9α,13α)-1-Chloro-4-hydroxy-6-isopropoxy-3-methoxy-17-methyl-5,6-didehydromorphinan-7-one

The title compound is obtained using the procedure described in Example 10 replacing absolute alcohol with isopropylic alcohol.

Melting point : 216-218°C.

EXAMPLE 24 : (9α,13α)-1-Chloro-3,7-dimethoxy-17-methyl-6-oxo-7,8-didehydromorphinan-4-yl chloroacetate

The title compound is obtained using the procedure described in Example 2 replacing propionic anhydrid with chloroacetic anhydrid.

Melting point :223-225°C.

PHARMACOLOGICAL STUDY OF COMPOUNDS OF THE INVENTION

EXAMPLE A : Acute toxicity study

Acute toxicity was evaluated after oral administration to groups each comprising 8 mice (26 ± 2 grams). The animals were observed at regular intervals during the course of the

first day, and daily for the two weeks following treatment. The LD_{50} (dose that causes the death of 50 % of the animals) was evaluated and demonstrated the low toxicity of the compounds of the invention.

EXAMPLE B : Morris water maze test in the mouse

The anti-amnesic effects of the compounds of the present invention have been evaluated using the Morris water maze test (Morris *et al.*, Nature,1986, 319, 774-776) in the mouse and scopolamine as amnesic agent. Kumming strain mice (18-24g, Shanghai Experimental Animal Centre) of either sex were used. Mice were placed on the water maze (80x50x20 cm) and trained to find the platform. Following the period of one day's habituation, each mouse received 3 daily training sessions for seven days. Mice were trained to a criterion of finding the platform within 20 seconds and with < 2 errors of entering a dead-end. Once a mouse met the criterion, training was reduced to one daily session until all mice met the criterion. Trained mice were randomly assigned to sub-groups. Compounds under study were dissolved in distilled water and administered by the oral route 40 minutes before behavioural testing. Scopolamine (5 mg/kg, i.p.) was injected 30 minutes before the test. The number of errors and the time for reaching the platform were recorded. Data were expressed as means +/- s.e.m. Statistical analysis was performed using ANOVA followed by Duncan's multiple-range test.

Results demonstrate that compounds of the present invention were capable of counteracting in a dose-dependent manner (from 20 to 100 mg/kg) scopolamine-induced memory impairments in the Morris water maze test in the mouse, indicating that such compounds possess anti-amnesic properties. As example, compound of Example 4 gave the following results :

{ Scopolamine : 0
Example 4 : 0 } ⇒ Latency to find the platform = 15 s

{ Scopolamine : 3 mg/kg
Example 4 : 0 } ⇒ Latency to find the platform = 55 s

{ Scopolamine : 3 mg/kg
Example 4 : 20 mg/kg } ⇒ Latency to find the platform = 35 s

{ Scopolamine : 3 mg/kg
Example 4 : 30 mg/kg } ⇒ Latency to find the platform = 25 s

EXAMPLE C : Social recognition in the Wistar rat

Initially described in 1982 by THOR and HOLLOWAY (J. Comp. Physiol., 1982, 96, 1000-1006), the social recognition test has subsequently been proposed by various authors (DANTZER *et al.*, Psychopharmacology, 1987, 91, 363-368 ; PERIO *et al.*, Psychopharmacology, 1989, 97, 262-268) for studying the mnemocognitive effects of new compounds. The test is based on the natural expression of the olfactory memory of the rat and its natural tendency to forget, and allows evaluation of memorisation, by recognition of a young congeneric animal, by an adult rat. A young rat (21 days), taken at random, is placed for 5 minutes in the cage housing an adult rat. With the aid of a video device, the experimenter observes the social recognition behaviour of the adult rat and measures its overall duration. The young rat is then removed from the adult rat's cage and is placed in its own cage until the second introduction. The adult rat is given the compound under test and, after 2 hours, is again brought into the presence (5 minutes) of the young rat. The social recognition behaviour is then observed again and its duration measured. The assessment criterion is the difference (T_2-T_1), expressed in seconds, between the "recognition" times of the 2 encounters.

The results obtained show a difference (T_2-T_1) ranging from (–10) s to (–36) s for doses ranging from 3 to 30 mg/kg, which shows that the compounds of the invention very greatly enhance memorisation. As example, compound of Example 13 at a dose of 20 mg/kg showed a difference (T_2-T_1) of – 36 s, and compound of Example 5 a (T_2-T_1) of – 31 s.

EXAMPLE D : Object recognition in the Wistar rat

The object recognition test in the Wistar rat was initially developed by ENNACEUR and DELACOUR (Behav. Brain Res., 1988, 31, 47-59). The test is based on the spontaneous exploratory activity of the animal and has the characteristics of episodic memory in humans. This memory test is sensitive to ageing (SCALI *et al.*, Eur. J. Pharmacol., 1997, 325, 173-180) and to cholinergic dysfunctions (BARTOLINI *et al.*, Pharm. Biochem. Behav. 1996, 53(2), 277-283) and is based on the differences in the exploration of 2 objects of fairly similar shape – one familiar, the other new. Prior to the test, the animals are habituated to the environment (an enclosure without an object). In the course of a first session, the rats are placed (3 minutes) in the enclosure, in which there are 2 identical objects. The duration of exploration is measured for each object. In the course of the second session (3 minutes), 24 hours later, 1 of the 2 objects is replaced by a new object. The duration of exploration is measured for each object. The assessment criterion is the difference, Delta, expressed in seconds, between the exploration times for the new object and for the familiar object in the course of the second session. The control animals, previously treated with the carrier by the IP route 30 minutes before each session, explore the familiar object and the new object in an identical manner, which indicates that the object introduced earlier has been forgotten. Animals treated with a compound that facilitates mnemocognition preferentially explore the new object, which indicates that the object introduced earlier has been remembered.

The results obtained show a difference, Delta, ranging from 5 to 11 s, for doses ranging from 0.3 to 10 mg/kg, which shows that the compounds of the invention greatly enhance memorisation. As example, compound of Example 4 showed a Delta of 10 s at a dose of 3 mg/kg.

EXEMPLE E : $NANO_2$ induced anoxia in mice

The neuroprotective effects of the compounds of the present invention have been evaluated in mice. Kunming strain mice of either sex were supplied by Shanghaï Experimental Animal Center, Chinese Academy of Sciences (Grade clear, Certificate N°005). Mice

weighing 22-28 g were kept in a 12 hours-light-dark cycle and given food and water *ad libitum*. Compounds under study were dissolved in a 5 % polysorbate-80 solution and orally administered (50 mg/kg) 60 minutes prior to the administration of $NaNO_2$ at a dose of 225 mg/kg *ip*. Lethality was observed and the prolongation of survival was recorded. The results obtained indicate that the compounds of the present invention were able to increase the survival of mice after an *ip* administration of $NaNO_2$. These results demonstrate that the compounds of the present invention possess patent anti-anoxic and neuroprotective effects in the mouse. As example, compound of Example 5 shows a prolongation of survival of 31 % at 70 mg/kg *p.o.*.

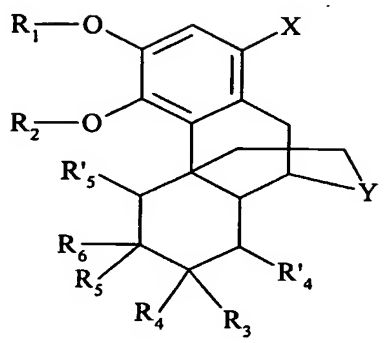
EXAMPLE F : Pharmaceutical composition

Formula for the preparation of 1000 tablets each containing 10 mg of active ingredient:

(9α,13α)-1-Bromo-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol ..... 10 g
hydroxypropylcellulose ..... 2 g
wheat starch ..... 10 g
lactose ..... 100 g
magnesium stearate ..... 3 g
talc ..... 3 g

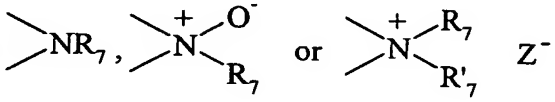
CLAIMS

1. Compounds of formula (I) :



(I),

wherein

- R_1 represents an alkyl group,
- R_2 represents a hydrogen atom or an alkylcarbonyl group, an haloalkylcarbonyl group or an arylcarbonyl group,
- Y represents a group 

wherein R_7 and R'_7, identical or differents, each represent an alkyl group, and Z^- represents a halogen anion,

- R_3 represents a hydroxy or alkoxy group,
- R_4 and R'_4 each represent a hydrogen atom or together form an additional bond, or R_3 and R_4 together form an oxo or =N-OR_8 group (wherein R_8 represents a hydrogen atom or an alkyl group),
- R_6 represents a hydroxy, alkylcarbonyloxy (wherein the alkyl moiety can be substituted by a hydroxy, alkoxy, carboxy or alkyloxycarbonyl group) or alkoxy group,
- R_5 and R'_5 each represent a hydrogen atom or together form an additional bond,

or R_5 and R_6 together form an oxo, =N-OR_9 or =N-$NR_{10}R_{11}$ group (wherein R_9, R_{10}, and R_{11}, which may be the same or different, each represent a hydrogen atom or an alkyl group),

- and X represents a halogen atom,

with the proviso that the compound of formula (I) cannot represent 1-bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one,

it being understood that

- "alkyl" means an alkyl group containing 1 to 6 carbon atoms which may be linear or branched,
- "alkoxy" means an alkyloxy group containing 1 to 6 carbon atoms which may be linear or branched,

to their enantiomers and diastereoisomers, and to addition salts thereof with a pharmaceutically acceptable acid or base.

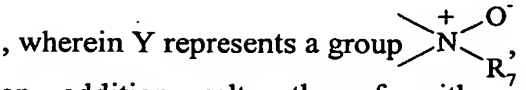
2. Compounds of formula (I) according to claim 1, wherein R_1 represents a methyl group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

3. Compounds of formula (I) according to claim 1, wherein R_2 represents a hydrogen atom, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

4. Compounds of formula (I) according to claim 1, wherein R_2 represents an alkylcarbonyl group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

5. Compounds of formula (I) according to claim 1, wherein R_2 represents an ethylcarbonyl group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

6. Compounds of formula (I) according to claim 1, wherein Y represents a group NR_7, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

7. Compounds of formula (I) according to claim 1, wherein Y represents a group  , their enantiomers and diastereoisomers, an addition salts thereof with a pharmaceutically acceptable acid or base.

8. Compounds of formula (I) according to claim 1, wherein X represents a chlorine atom, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

9. Compounds of formula (I) according to claim 1, wherein X represents a bromine atom, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

10. Compounds of formula (I) according to claim 1, wherein R_3 represents an alkoxy group, and R_4 and R'_4 together form an additional bond, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

11. Compounds of formula (I) according to claim 1, wherein R_5 represents a hydrogen atom, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

12. Compounds of formula (I) according to claim 1, wherein R_6 represents an OH group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

13. Compounds of formula (I) according to claim 1, wherein R_6 represents an alkylcarbonyloxy group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

14. Compounds of formula (I) according claim 1, wherein R_5 and R_6 together form an oxo group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

15. Compounds of formula (I) according claim 1, wherein R_5 and R_6 together form a $=N-OH$ group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

16. Compound of formula (I) according to claim 1, which is (9α,13α)-1-chloro-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol.

17. Compound of formula (I) according to claim 1, which is (9α,13α)-1-chloro-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate.

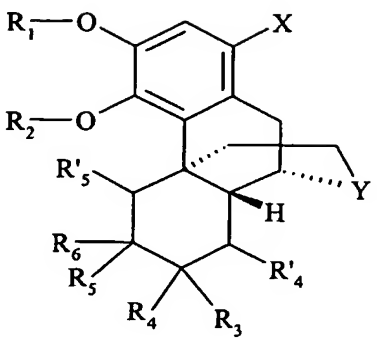
18. Compound of formula (I) according to claim 1, which is (9α,13α)-1-Bromo-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol.

19. Compounds of formula (I) according claim 1, which is (9α,13α)-1-Bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7;8-didehydromorphinan-6-one oxime.

20. Compounds of formula (I) according claim 1, which is (9α,13α)-1-Bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide.

21. Compounds of formula (I) according claim 1, which is (9α,13α)-1-Chloro-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide.

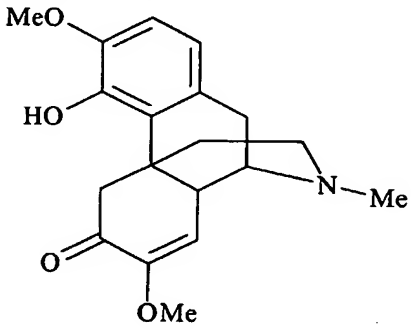
22. Compounds of formula (I) according to claim 1, having the configuration shown by formula (I') :



(I')

and addition salts thereof with a pharmaceutically acceptable acid or base.

23. Process for the preparation of compounds of formula (I) according to claim 1, characterised in that there is used as starting material the compound of formula (II) :



(II),

obtained by extraction starting from the stem of *Sinomenum acutum* according to Figure 1 below :

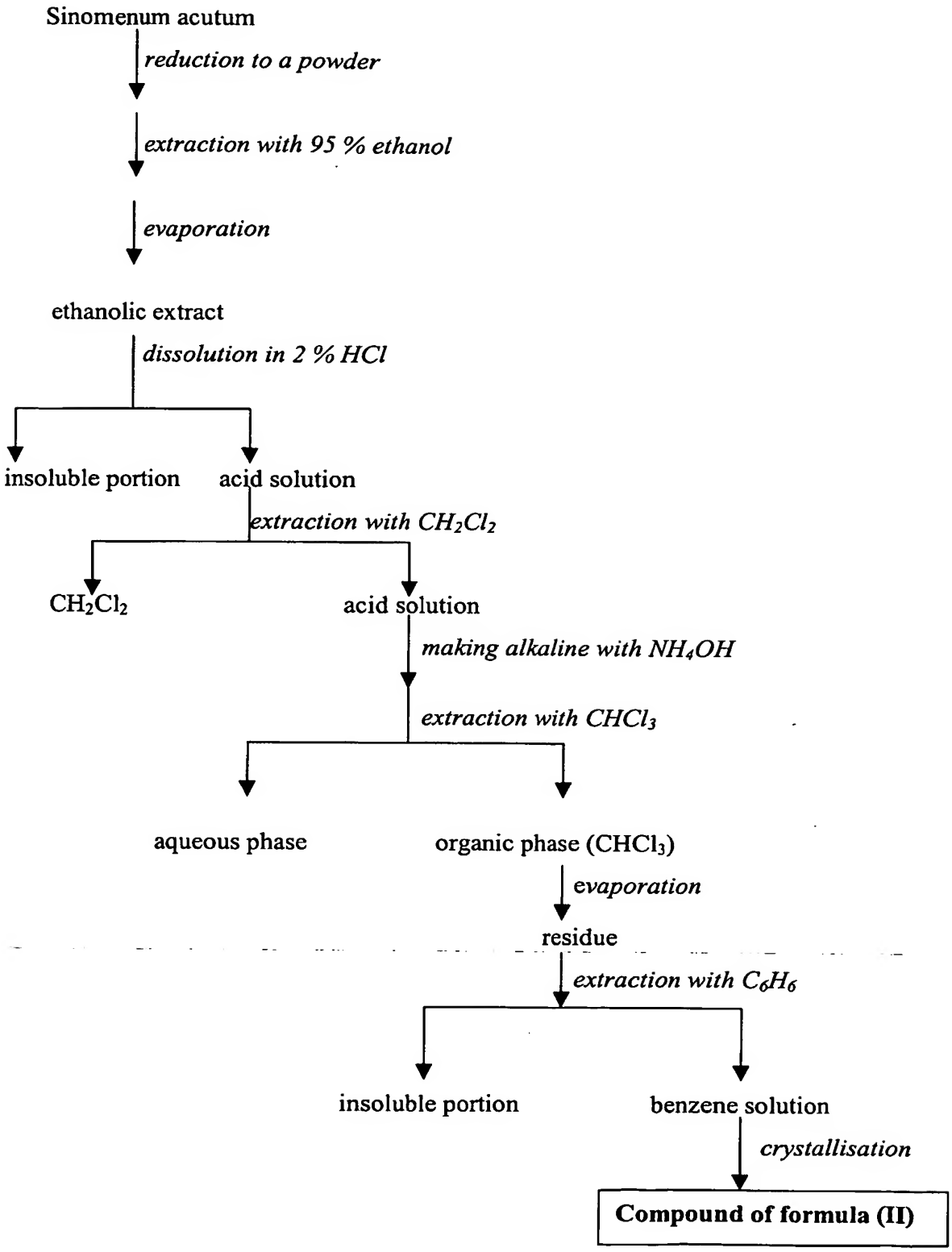
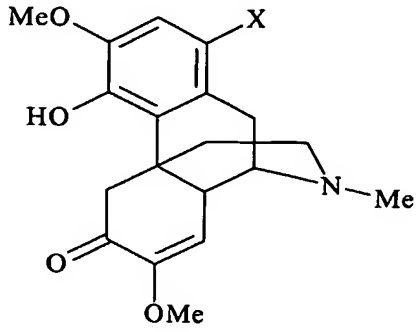


Figure 1 *: Extraction of the compound of formula (II)*

which is subjected to the action of a halogenating agent such as SO_2Cl_2 or Br_2 to obtain the compound of formula (I/a), a particular case of the compounds of formula (I):



(I/a),

wherein X is as defined for formula (I), which compound of formula (I/a) is subjected to conventional chemical reactions to obtain the totality of the compounds of formula (I), which may be purified according to a conventional separation technique, are converted, if desired, into their addition salts with a pharmaceutically acceptable acid or base and are separated, where appropriate, into their isomers according to a conventional separation technique.

24. Pharmaceutical compositions comprising at least one compound of formula (I) according to any one of claims 1 to 22 or an addition salt thereof with a pharmaceutically acceptable acid or base, in combination with one or more pharmaceutically acceptable excipients.

25. Pharmaceutical compositions according to claim 24 for use in the manufacture of medicaments for the treatment of deficiencies of memory associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

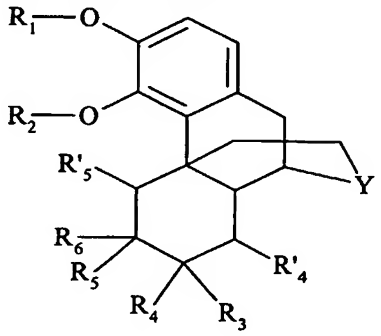
26. Use of sinomenine and/or sinomenine compounds in obtaining pharmaceutical compositions intended for the treatment of deficiencies of memory associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease,

Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

27. Use, according to claim 26, of sinomenine in obtaining pharmaceutical compositions intended for the treatment of deficiencies of memory associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

28. Use, according to claim 26, of sinomenine compounds in obtaining pharmaceutical compositions intended for the treatment of deficiencies of memory associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

29. Use, according to claim 26, of sinomenine compounds of formula (Ia) :



(Ia),

wherein R_1, R_2, R_3, R_4, R'_4, R_5, R'_5, R_6 and Y are as defined in claim 1, in obtaining pharmaceutical compositions intended for the treatment of deficiencies of memory associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

30. Use, according to claim 26, of sinomenine compounds that are: (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one hydrazone; (7α,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; (7β,9α,13α)-4-hydroxy-3,7-di-

methoxy-17-methylmorphinan-6-one; (9α,13α)-3,7-dimethoxy-17-methyl-6-oxo-7,8-didehydromorphinan-4-yl propionate; (9α,13α)-3,4,7-trimethoxy-17-methyl-7,8-didehydromorphinan-6-one; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime; (9α,13α)-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide; (9α,13α)-6-amino-3,7-dimethoxy-17-methylmorphinan-4-ol; 4-{[(9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl]-oxy}-4-oxobutanoic acid; (9α,13α)-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate (9α,13α)-17-benzyl-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-17-ium-6-one bromide; (9α,13α)-17-ethyl-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-17-ium-4,6-diol bromide; (9α,13α)-17-ethyl-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-17-ium-6-one bromide; (9α,13α)-4-(benzoyloxy)-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl benzoate; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl benzoate; (9α,13α)-6-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4-yl benzoate, in obtaining pharmaceutical compositions intended for the treatment of deficiencies of memory associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

31. Pharmaceutical compositions comprising sinomenine or a sinomenine compound, in combination with one or more pharmaceutically acceptable excipients, for use in the treatment of deficiencies of memory associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14841

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D221/28 C07D489/00 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IIJIMA I ET AL: JOURNAL OF MEDICINAL CHEMISTRY, vol. 21, no. 12, 1978, pages 1320-1322, XP002273127 Scheme I	1-3,7, 9-11,14
A	WHITE, JAMES D. ET AL: "Biomimetic total synthesis of (-)-codeine" TETRAHEDRON , 39(14), 2393-7 CODEN: TETRAB; ISSN: 0040-4020, 1983, XP002273128 See compounds 9-12	1
A	US 4 912 114 A (REVESZ LASZLO) 27 March 1990 (1990-03-27) column 1, line 10 - column 1, line 62 column 20, line 4 - column 20, line 21	1-31

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2004	26/03/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Usuelli, A

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14841

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 661 283 A (TORAY INDUSTRIES) 5 July 1995 (1995-07-05) page 3, line 6 - page 4, line 37	1-31

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/14841

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		DE 69414085 D1	26-11-1998
		DE 69414085 T2	18-03-1999
		EP 0661283 A1	05-07-1995
		WO 9503307 A1	02-02-1995
		TW 401400 B	11-08-2000
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